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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/042,614	01/09/2002	Ya Fang Liu	YFLU-P03-001	6176

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EXAMINER
HANLEY, SUSAN MARIE

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 06/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/042,614	LIU, YA FANG	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,34 and 44-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,34 and 44-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/4/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Claims 33, 34 and 44-46 are pending.

Applicant's arguments filed August 4, 2004 are moot in light of new rejections.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The IDS filed 8/4/04 has been considered again because the Examiner failed to initial document DB* on page 2 of the IDS. The omission has been corrected.

Claim Rejections - 35 USC § 112

Claims 33, 34 and 44-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of assessing a compound's ability to inhibit JNK kinase in a susceptible mammal by administering the compound to a mammal, harvesting neuronal tissue sample and determining apoptosis, wherein the result of testing for apoptosis is coupled with another test that confirms that the compound is a JNK kinase inhibitor, does not reasonably provide enablement for assessing a compound's ability to inhibit JNK kinase in a susceptible mammal by administering the compound to a mammal, harvesting neuronal tissue sample and determining apoptosis without an additional method of confirming that the compound is an inhibitor of JNK kinase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method of assessing a compound's ability to inhibit JNK kinase in a susceptible mammal by administering the compound to a mammal, harvesting neuronal tissue sample and determining apoptosis in said tissue sample. Dependent claims are drawn to types of JNK kinase and methods of determining apoptosis by TUNEL assay, labeling c-Jun with P-32 or staining.

The specification discloses that known JNK inhibitors can be administered to a mammal, after which the animal in sacrificed and apoptosis is determined by TUNEL or staining (p. 17, lines 16-28). Thus, the claimed method is enabled only when one knows *a priori* that the test compound is a JNK kinase inhibitor. The specification teaches methods of separately determining the ability of a compound to inhibit JNK kinase by radioassays with cJUN.

Fadeel et al. recently reviewed the current model of apoptosis signaling. The model is complex and shows that the activation of kinases is not the only cellular mechanism that initiates apoptosis. Caspase activation, ceramide, DNA damage and mitochondrial action can also cause an apoptoic event (p. 701, Fig. 1).

The specification fails to provide guidance that would enable a person of skill in the art to determine if the inhibition of apoptosis is the mechanism by which a test compound works without knowing that the test compound was an inhibitor of JNK kinase *a priori*. The prior art clearly demonstrates that, in addition to kinase activation, a number of pathways regulate apoptosis in a cell. Therefore, it is essential that the skilled artisan know that the test compound is a JNK kinase inhibitor before concluding that the test compound inhibited apoptosis by decreasing JNK kinase activity. Otherwise, the skilled artisan can only conclude that the test compound inhibits apoptosis since the compound could effect inhibition by a number of pathways. Hence, the measurement of inhibition of apoptosis in a mammal is simply a measurement apoptoic activity without context as to the molecular mechanism in the cell that initiates apoptosis.

Regarding claim 45, the labeling of c-Jun with P-32 phosphate is method to determine JNK kinase activity but does not necessarily connect the inhibition of JNK kinase with apoptosis. As discussed *supra*, the prior art clearly demonstrates that, in addition to kinase activation, a number of pathways regulate apoptosis in a cell. Therefore, it is essential that the skilled artisan measure apoptosis by an independent method before concluding that the test compound inhibited apoptosis due to the inhibition of JNK kinase activity by the method of claim 45.

There is no reliable method that predicts what intracellular apoptosis mechanism is being measured by the instant method unless the skilled artisan has been provided a context such as knowing if the test compound is known inhibit apoptosis by inhibiting JNK kinase activity. The measurement of cellular apoptosis does not, by itself, provide any information about the molecular mechanism by which apoptosis is occurring. Similarly, the measurement of JNK kinase activity does, by itself, determine if said JNK kinase inhibition is also a measure of apoptosis. The specification does not teach how one of skill in the art could decide *a priori* what apoptoic pathway was being measured by the instantly claimed method unless additional information was provided *supra*. The limited disclosure cannot be extrapolated by the skilled artisan to predict if a cell was experiencing inhibition of apoptosis due to the inhibition of JNK kinase, or *visa versa*, unless she or he had additional information such as that discussed *supra*. It would require one of skill in the art undue experimentation to determine if a cell was experiencing inhibition of apoptosis due to the inhibition of JNK kinase unless she or he had additional information according to the directions of the instant disclosure. Thus, claims 33, 34 and 44-46 are not commensurate in scope with the enabling disclosure.

As noted in the Office action of 11/4/04, Applicant has been given benefit of the filing date of the parent application 09/156,367, filed 9/17/98, but has been denied benefit to the provisional filing date of 5/14/98 for 60/085,439. New prior art has come to light that predates the parent date of 9/17/98.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 33 and 34 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Huan et al. (1996, abstract) in light of Finiels et al. (1995) and Borasio et al. (May 1998).

Huan et al. disclose that excitotoxin was administered to rats. Excitotoxin induced the death of neurons in the basal forebrain. The compound CEP-1347 was also administered to the rats prior to the injection of excitotoxin. Cell counting showed that CEP-137 protected neurons in the forebrain from excitotoxin-induced cells death.

Finiels et al. disclose that one of the properties inherent to excitotoxin is that it induces neuronal apoptosis (abstract).

Borasio et al. teach that one of the properties inherent to CEP-137 is that it inhibits JNK kinase (abstract). Although Borasio et al. was published less than one year prior to the effective filing date of the instant application, Borasio et al. teach a property that is an inherent part of the compound at the time of the use of the compound.

The disclosure by Huan et al. meets the limitations of instant claims 1 and 2 because CEP-137, which inherently inhibits JNK kinase, is administered to rats. The rats are susceptible to a neurological condition because they receive excitotoxin which induces neural apoptosis. After the administration of the CEP-137, Huan et al. teach that forebrain cells are counted to assess cell death. Huan et al. do not explicitly teach that the rats were sacrificed. However, this is an inherent step because an animal must be sacrificed in order to count cells. Since excitotoxin induces apoptosis, Huan et al. were measuring neuronal cell death due to apoptosis.

The disclosures by Finiels et al. and Borasio et al. are properly used to demonstrate inherent properties of compounds.

> MPEP 2112.02: PROCESS CLAIMS - PRIOR ART DEVICE ANTICIPATES A CLAIMED PROCESS IF THE DEVICE CARRIES OUT THE PROCESS DURING
> Under the principles of inherency, if a prior art device, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art device. When the prior art device is the same as a device described in

the specification for carrying out the claimed method, it can be assumed the device will inherently perform the claimed process. In re King, 801 F.2d 1324, 231USPQ 136 (Fed. Cir. 1986) See also In re Best, 562F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977) Ex parte Novitski, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993

Further, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

The disclosure by Finiels et al. and Borasio et al. are supporting references and properly used in a rejection under of U.S.C. 102 since they describe inherent properties of compounds. MPEP 2131.01.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33, 34, 44 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huan et al. (1996, abstract), Finiels et al. (1995) and Borasio et al. (April, 1998) in view of Liu (1997).

The combined disclosures by Huan et al., Finiels et al. and Borasio et al. are discussed *supra* and teach a method for decreasing apoptosis in neuronal cells by assessing cells death that is induced by an apoptosis-inducing agent, excitotoxin.

The combined disclosures do not teach using TUNEL and staining of cells with the dye Hoechst 33342 to assess apoptosis.

Liu et al. disclose that TUNEL and the staining of cells with Hoechst 33342 is a common alternative to determine neuron apoptosis (p. 5396, left column, see Histopathology section).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ TUNEL and staining of cells with the dye Hoechst 33342 to assess apoptosis in the method of Huan et al. The ordinary artisan would have been motivated to do so because the application of TUNEL and staining of cells with the dye Hoechst 33342 are equivalent alternatives to the method employed by Huan et al. for assessing neuronal apoptosis. The ordinary artisan would have had a reasonable expectation that TUNEL and staining of cells with the dye Hoechst 33342 could be used to assess apoptosis in the method of Huan et al. because they demonstrated that TUNEL and staining of cells with the dye Hoechst 33342 successfully assess apoptosis in neurons.

Claims 33, 34 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maas et al. (April 1998) in view of Huan et al. (1996) and Finiels et al. (1995).

Maas et al. disclose that withdrawal of neurotrophic support from rat retinal and PNS (chick sympathetic) neurons induces apoptosis in cell culture. Apoptosis can be rescued by the administration of olomoucine. The apoptosis-inhibiting property of olomousine was correlated with its in vitro IC50 for JNK kinase 1 and its potency to repress c-jun induction in live PC12 cells (abstract). Apoptosis was assessed by TUNEL assay and staining by Hoechst dye 33258 (p. 1403, left column, section for Staining procedures for apoptosis detection).

Maas et al. do not disclose the administration of a JNK inhibitor to a live animal that is susceptible to or has a neurological condition, harvesting neuronal tissue, determining apoptosis in the tissue sample and correlating the degree of apoptosis with the ability of the compound to inhibit JNK kinase.

The disclosures by Huan et al. and Finiels et al. are discussed *supra*. Briefly, the combined disclosures disclose that the compound CEP-1347 was administered to rats and inhibited the induction of apoptosis induced by excitotoxin.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the JNK inhibitor taught by Maas et al. to live rats, in the in vivo assay taught by Huan et al. to assess the anti-apoptoic activity of said JNK inhibitor. The ordinary artisan would have been motivated to do so because compounds that inhibits JNK kinase are potential treatments for neurodegenerative conditions such as Alzheimer's disease. The ordinary artisan would have had a reasonable expectation that the JNK kinase inhibitor taught by Maas et al. could be tested by the assay of Huan et al. because it has been shown to inhibit apoptosis in vitro.

Claims 33, 34, 44 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maas et al. (April 1998), Huan et al. (1996) and Finiels et al. (1995) in view of Liu (1997).

The combined disclosures by Borasio et al. and Huan et al., Finiels et al. are discussed *supra* and teach a method for screening JNK kinase-inhibiting compounds in vivo for decreasing apoptosis in neuronal cells by assessing apoptosis by TUNEL or Hoechst dye 33258.

The combined disclosures do not teach using Hoechst dye 33342 to assess apoptosis.

Liu et al. disclose that TUNEL and the staining of cells with Hoechst 33342 is a common alternative to determine neuron apoptosis (p. 5396, left column, see Histopathology section).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the dye Hoechst 33342 to assess apoptosis in the modified method of Borasio et al. The

ordinary artisan would have been motivated to do so because the application of the dye Hoechst 33342 to assess apoptosis is equivalent alternative to the use of Hoechst 33258 for assessing neuronal apoptosis. The ordinary artisan would have had a reasonable expectation that the dye Hoechst 33342 could be used to assess apoptosis in the modified method of Borasio et al. because Liu et al. demonstrated that the staining of cells with the dye Hoechst 33342 successfully assess apoptosis in neurons.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JEAN C. WITZ
PRIMARY EXAMINER